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Evolution

Suggested model for prebiotic evolution: The use of chaos

(origin of life/spin glass)

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ABSTRACT **I elaborate on an earlier model for prebiotic evolution by adding a selection function depending randomly on base-pair correlations along the replicating RNA chains. By analogy with the equilibrium statistics of spin glass, this should give a wide variety of metastable "species" that can mutate or combine symbiotically.**

Problems of Prebiotic Evolution. Anderson and Stein (1) have reported an attempt to model the first crucial stages in the evolutionary process, those stages in which the first information-containing molecules appear. There are of course many points in the process that led from inanimate matter to life as we know it that could be called crucial, and few of them have been investigated far enough that one can see a clear resolution of their manner of occurrence on the actual early earth. It has seemed, however, and I feel that on this point several previous investigators agree [e.g., Eigen (2, 3), Orgel (4, 5), and others], that the central question is that discussed in ref. 1: From essentially uniquely characterized simple molecules, which even when autocatalytically generated do not have any resemblance to a self-replicating information string such as is necessary if evolutionary choice is to begin to operate, how can such information strings develop?

The other important stages are as follows. First, the synthesis of a sufficient concentration of primitive organic molecules—phosphates, amines, purines and pyrimidines and such—and their activation into states capable of polymerizing into large molecules: investigations (6, 7) have suggested that, in the energy-rich environment of the primitive earth, moderately complex organic molecules can appear, but certainly no unique pathway has been proven. Nonetheless, this process is a purely chemical kinetic problem, and it seems likely that there were, in the enormous variety of microenvironments available on the early planet, many occasions for the collection of an organic soup having considerable concentrations of such molecules in energy-rich forms. No question of principle seems to be involved here.

I choose to separate the next stage into two parts, in contradiction to Eigen (2, 3) who favors the simultaneous appearance of nucleic acids and proteins. I cannot see how the enzymes can have evolved simultaneously with the nucleic acid chains, because these are structurally unrelated molecules and both of great complexity. Peptides can easily have been chemically involved—say as terminations—with the first nucleic acid chains, but I believe the "code" must have evolved quite separately and later. The code could even be a consequence of symbiosis of very primitive tRNA-like organisms (8, 9). The coupling of nucleic acid chains and proteins to produce the code is then a third event, which to my eye contains serious questions of probability and of detail but ones unaffected by the questions of principle I will discuss here. This point of view is made more reasonable by the fact that RNA is used for purely structural purposes both in ribosomes and, of course, in tRNA itself, so it is not true that *all* biological catalysts are proteins.

All life now lives within a cell membrane—even where, as with the $Q\beta$ phage, it has little of the other paraphernalia of normal organisms, even dispensing with DNA and not using host enzymes to replicate. Many vital processes involve the membrane structurally. The cell membrane must have appeared early, but I see no difficulty with the idea that it initially appeared as an entirely separate construct in the environment and only later was manufactured as a substitute for natural lipid layers, or even was evolved or co-opted to allow the living molecules to grow elsewhere than the pores in clays or rocks in which they may have first appeared. Lipid membrane is an equilibrium structure, not a dissipative one in any sense, and for the primitive chemical species to fold it around themselves is not an implausible step.

In the final section of this paper I will discuss some of the alternative approaches more fully, after my own ideas are before the reader. Let me now proceed directly to what I consider to be the problems.

Some Quasi-Philosophical Questions. Living organisms may be the only stable example of the (essentially philosophical) concept called "dissipative structures." As Haken and others (refs. 10 and 11 and refs. cited therein) have emphasized, most of the structures we encounter in nature are "equilibrium structures": at the microscopic level, such broken symmetry structures as crystals, magnetic domains, liquid crystals, and lipid membranes; at the macroscopic level, rocks, stars, and planets. They have postulated a second type of structure, organized not as a consequence of equilibrium thermodynamics, but rather as a result of a sufficiently large deviation from equilibrium forcing a driven system that is very far from equilibrium into some kind of organized state. The more we study systems that appear to do this the more we recognize that *stable* organized dissipative structures are very much the exception rather than the rule. Even the simplest driven dynamical systems are liable to evolve into a chaotic state. The example Prigogine (11), for instance, has most often described, the Benard convection cell, has recently been shown to be intrinsically chaotic under almost all conditions (12). Whatever dissipative structures exist are surely remarkably restricted in their domain of stability, quite unlike living entities.

For these reasons, I believe that the concept of dissipative structures, as it has been elucidated so far, may not be relevant to the origin of life. In any case, it is by no means sufficient, in discussing the question of whether "chance and necessity" can really lead to life, to point to the case of bifurcations in dissipative systems as an example of organized structure. We must ask for more.

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CONSTRUCTION OF THE MODEL

I focus here on two aspects of life on which previous models have not been satisfactory to me: *stability* and *diversity*.

It is easy to invent a model that can produce a great diversity of different "polynucleotides" if one neglects the real complications of the chemistry of these molecules. The scheme proposed in ref. 1 had this property. We used two complementary "bases", which we called A and B (modeled really on guanine and cytosine), and treated them as totally equivalent "letters" in a binary alphabet. By setting up a kinetics in which strings of letters A-B-A-A ... catalyze the formation of the complementary structure B-A-B-B ... by the Crick–Watson conjugation process, one can arrive at strings of arbitrary length and complexity. Unfortunately, there is no particular reason why any outcome of this process will remain stable in any particular structure. We encountered this difficulty very early in our computations, in the fact that we could not in any way evaluate what we could call "success": we could not identify *when* a "species" had evolved, because all species were equivalent and could presumably mutate at will into each other. As far as we carried our calculations, which may not have been adequate, we found simply a chaotic mass of rather unrelated strings. This is the case when *stability* is absent: any one species will mutate into any other.

It is equally easy to set up a process with a stable result but only at the expense of losing a crucial degree of *diversity*. There are two simple ways to do this. One is to take into account the genuine and real difference in local free energy between different groupings of bases. For instance, it seems likely that G-C-G-C-G-C ... is a very stable polymer. If, in our A-B model, we inserted a strong preference for A-B pairing, we could get a system that could very stably grow in the A-B-A-B ... mode and nothing else. Any *one* stable structure is uninteresting because, essentially, it contains no information: there is no diversity on which evolution can build to create ever more complex structures.

I have a sense that this is the fate of almost any simple realization of Eigen's idea of the complex autocatalytic cycle. Such a cycle is likely to be so specific that it permits only one outcome (or, if certain simple symmetries such as reflection are involved, two at most). Virtually all the seriously proposed mechanisms so far suggested are caught in this difficulty.

Stability and diversity together are the key, and this suggested the one system in equilibrium statistical mechanics that has both of these properties: the spin glass. This possibility was suggested by Hopfield's ideas on associative memory, available in preprint form. (Discussions with Hopfield have been most useful.) The spin glass is a magnetic system that has the conventional-looking spin Hamiltonian,

$$\mathcal{H} = -\sum_{i,j} J_{ij} S_i S_j \qquad [1]$$

but the exchange integrals J_{ij} are random functions of the pair of variables (i,j), which take on both positive and negative values. The key element in the Hamiltonian that makes the substance a spin glass is the property of "frustration," which is slightly ill-defined (13, 14) but means that there are many loops (cycles) for which $(J_{ij} J_{jk} J_{kl} \dots J_{mi})$ is *negative*, so that all of the interactions in the loop cannot be satisfied simultaneously. If there are as many such frustrated cycles as there are acceptable ones, the state becomes highly degenerate, and it seems there are very large numbers of states that are local minima of the energy, not far in energy from the largest one or ones and essentially different each from the other. The number of such states seems to increase exponentially with the number of spins (15). It has been shown (16) that in some models—specifically when J_{ij} is nonzero for a very large number $M \gg 1$ of other spins j—the relaxation between different metastable states is extremely slow. These different metastable states have the required properties of stability and diversity in the equilibrium case.

A number of conditions for the existence of stable spin glass states are worth noting. In the first place, if we are to model a system involving base-pair conjugation on a linear RNA chain, we will map the spins S_i onto the bases: let us initially set guanine = +, cytosine = −, for instance; later, we can give S_i more values if we choose. Then the "system" must be a linear chain of spins S_i of some length N. It is essential that J_{ij} be *long-range*; otherwise, even the equilibrium structure is not stable [the condition as $N \to \infty$ is $J_{ij} \propto 1/(i-j)$]. Most particularly, J_{ij} must not be a simple short-range function of $(i-j)$; otherwise, the gound state is periodic and hence, by our definition, trivial. In fact, if we choose M and N comparable, both problems are solved, so that is the model we shall use. Without these restrictions, we have not a hope of producing appropriate objects.

How are we to understand the appearance of such properties in some realistic early world? What we have not yet done is to take into account adequately the complex chemistry of the RNA polymer system. There are a number of kinetic as well as equilibrium restraints on the system that have not been taken into account: I list a few that are already known (17, 18): (*i*) Poly(G) is probably the strongest bound of all polymers, but it has the unfortunate property of self-conjugating in four-strand helices. Thus, any appreciable length of parallel *S* [implying poly(G) G-G-G-G ... for at least one of the conjugate pairs] is not viable. (*ii*) After a length of four or five bases, RNA can fold back on itself and self-conjugate. Thus any appreciable length of G-C-G-C ... or in fact any self-conjugating sequence such as C-C-G-G-C-C-G-G is not viable as far as reproduction is concerned. This is a very strong restriction, because it implies that these sequences must not occur anywhere along the chain and is hence the equivalent of very long-range interactions. (*iii*) The ends are special points with very-long-range implications because, in real systems, they will surely be attached to either substrate or peptides. For instance, in Orgel's present experiments, he finds that chains of 13, 25 or 26, and possibly about 39 bases are particularly stable, probably because the helix repeat distance is 12 bases and the chain is growing at a flat surface. (*iv*) Coupling to peptides can occur in several ways. The simplest is chain termination and, if the peptide is polymerized to any appreciable length, it can influence catalysis at quite distant sites along the RNA chain. Another form of coupling is the replacement of a RNA base by intercalation of an aromatic ring from an amino acid. Of course, once the code or its primitive predecessor starts to evolve, this provides a very effective long-range correlation between distant sites along the RNA chain. The random frustrated model is perhaps an even better one for evolution at a more advanced stage. (*v*) Finally, the environment can contain many other influences that appear random or chaotic from the point of view of a growing RNA chain. Any periodic crystal structure of a substrate, or any periodic structure of a lipid membrane in or near which the RNA is growing, would have a chaotic-looking influence on the RNA, except in the infinitely unlikely case that the periodicity of the substrate matched one of the two periods (base spacing or helix repeat) of the RNA.

This is only a partial list of the possible types of essentially conflicting influences that will affect the growth or survival rates of an autocatalyzing RNA chain. Let me summarize the effects of all such environmental factors on the RNA chains by a death function

$$D_N(S_1 \dots S_N) \qquad [2]$$

for chains of length N. As in previous work, I assume a regular fluctuation of temperature that periodically breaks apart and re-forms conjugated pairs of nucleic acid (NA) chains. I introduce a distribution of chains of all possible lengths,

$$\rho(t, S_1, S_2, S_3 \ldots S_N) \quad [3]$$

and the death function gives the difference in ρ caused by environmental factors

$$\Delta\rho_{\text{env}} = \rho(t + \Delta t; S_1 \ldots S_N) - \rho(t, S_1 \ldots S_N) = -D(S_1 \ldots S_N)\rho. \quad [4]$$

In the actual primitive system, as well as in the simulation, we can define D and ρ only probabilistically. D represents the *probability* per cycle of death of a particular exemplar $(S_i \ldots S_N)$.

We assume that D is a chaotic random function of all its arguments. Noting that $S_i^{2N} = 1$, $S_i^{2N+1} = S_i$, D is necessarily linear in all S_i and can be expanded in successive correlations between its arguments:

$$D_N = \sum_i h_i^N S_i + \sum_{i \neq j} J_{ij}^N S_i S_j + \sum_{i \neq j \neq k} C_{ijk}^N S_i S_j S_k \ldots. \quad [5]$$

Now it is likely that $h_i = 0$, because the conjugation mechanism imposes population symmetry between cytosine and guanine at every site in detail. Whenever guanine appears, in the next generation (if the system is to be viable), cytosine must appear and vice versa. Thus expansion **5** starts with J_{ij}, and we shall for simplicity cut it off at this term as well. This is a rather cavalier step and only justifiable as a heuristic hypothesis about the nature of such random functions, which must be discussed. Imagine a minimum of the D function in which the various "spins" have values S_i. We can imagine changing a few of the bases $S_i \rightarrow -S_i$ and making an expansion such as **5**, in which we can think of the coefficients as a kind of partial derivative: $h_i = \Delta D/\Delta S_i$, $J_{ij} = \Delta^2 D/\Delta S_i \Delta S_j$, etc. These coefficients will now be functions of all the other values of S but near a particular D minimum they will not be strong functions because each base interacts with many (N) others and, in particular, C_{ijk} will be $\sim 1/N^{1/2}$ of J_{ij}, etc. Thus, locally the behavior will be like that of the truncated series. In particular, because of conjugation symmetry, there will be many minima, even locally. Moving from one minimum to another quite far away, we will not expect the values of J_{ij} to remain constant but since, for the spin glass, we know there to be $0\,(e^N)$ local minima, and a large number of these to be quite deep, the local expansion will include at least a relatively large number of local minima. More generally, there seems to be a new class of functions of many variables of which the spin-glass Hamiltonian is an example and of which our desired D function may be another—as is, perhaps, the length of a "traveling salesman" tour, according to the work of Kirkpatrick *et al.* (19). I would like to call these generally "frustrated random functions." It is hoped that the appropriate survival functions for evolution problems have this frustrated random character and thus are best modeled by a spin-glass function; but of course a more theoretical proof of such a vague concept is out of the question. Thus, I take

$$D_N = \sum_{i \neq j}^{N} J_{ij}^N S_i S_j \quad [6]$$

and in fact it is almost certainly adequate to assume that J_{ij} is independent of N.

Note the very important role played by the symmetry of the conjugation mechanism for the simplification of **5** to **6**. This is crucial. The properties of random field models are totally different from those of spin glasses and much less interesting. In particular, they usually have a unique stable solution, at least when the random field is large enough and, in the present case, that is a disaster because it means that no information is generated. Most other simple (or complex) autocatalytic cycles do not seem to me to have this property that is so vital. It is perhaps even a bit disturbing to have to suggest that Crick–Watson base-pair conjugation—or at least the concept of complementary strings—may be absolutely and uniquely essential in getting life started.

Orgel has pointed out that my use of conjugation symmetry to eliminate the "random-field" case of $h_i \neq 0$ is suspect. This was a key part of the argument because I see it as essential that the death function have many nearly equivalent minima whereas, with large random fields h_i, the solution tends to be unique. The problem is that conjugation acts to reverse the order of the bases—i.e., that $3' \rightarrow 5'$ is replicated on $5' \rightarrow 3'$ and hence is reversed in order. Thus G·C produces the identical G·C not the symmetric C·G.

The following argument arose in a discussion with D. S. Rokhsar. The fact that replication of a chain of length L produces $-S_{L-i}$ from S_i can be expressed by adding the two symmetry-related death functions

$$D_{\text{eff}}(S_i) = D(S_i \ldots) + D(-S_{L-i}).$$

We now expand linearly in S_i and get

$$D_{\text{eff}}(S_i) = \sum_i h_i(S_j) S_i + h_i(-S_{L-j})(-S_{L-i}),$$

where the second h_i is the same function of the variables $-S_{L-j}$ as the first one is of S_j. In particular, if h_i has an average value, $\bar{h}_i$, we can write

$$D_{\text{eff}}(S_i) = \bar{h}_i(S_i - S_{L-i}) + S_i[h_i(S_j) - \bar{h}_i] + S_{L-i}[h_i(-S_{L-j}) - \bar{h}_i].$$

This means that the random field acts on the variable $\sigma_i = S_i - S_{L-i}$, which has values 0, ± 2. If $|\sigma_i| = 2$, $S_i = -S_{L-i}$. In a state in which all $\bar{h}_i$ are large and control the structure, $S_i = -S_{L-i}$ and the polymer is self-conjugate: it can fold up and conjugate with itself.

This may be favorable under some circumstances, but I have already argued that such a polymer under most circumstances cannot reproduce, because it will fold and conjugate with itself rather than build a new version from smaller polymers. Because we can expect nature to have tried all possible rules and death functions, we are free to hypothesize that the majority of the $\bar{h}_i$ must be nearly zero to prevent self-conjugation or, equivalently, that the death function is approximately symmetric to order reversal as well as to conjugation. This implies that the terms in expansion **5** are only of second, fourth, etc., order. I note that empirically (and even theoretically) a small random field does not destroy the frustration property.

Now I will set up the remainder of the model for prebiotic evolution. This part closely resembles the model on which the previous, rather primitive, calculations were based and is reasonably conventional by now. I assume the following. (*i*) The environment is capable of supplying a continuous stream of high-energy guanine and cytosine monomers. Mathematically, we write this as

$$\Delta\rho_{\text{source}}(S_1 = \pm 1) = +s, \quad [7]$$

where the source s is chosen arbitrarily and more or less sets the time scale. (*ii*) At the beginning, there is a fortuitous density

of short polymers, so that conjugation will have a point from which to start: $\rho_{\text{initial}}(S_1S_2S_3)$, say, = finite for several values of $S_1S_2S_3$ including sign changes. (*iii*) Temperature is cycled so as to form and break up conjugate pairs at intervals Δt. When chains are conjugated in a contiguous fashion, they will polymerize (any failure to do so can be ignored as a nonevent or included in the death rate D). Thus, we envisage processes such as

$$\left.\begin{matrix}(-\ -\ -\ +);\ \ (-\ +\ +\ +\ +\ -)\\ (+\ +\ -);\end{matrix}\right\}\rightarrow\left\{\begin{matrix}(+\ +\ -)\ \ (-\ -\ -\ +)\\ (-\ +\ +\ +\ +\ -)\end{matrix}\right\}\rightarrow(+\ +\ -\ -\ -\ -\ +);\ \ (-\ +\ +\ +\ +\ -) \qquad [8a]$$

or more simply

$$(-);\ \ (+);\ \ (-);\ \ (+\ -\ -\ +)\rightarrow\left\{\begin{matrix}(-)\ (+)\ (-)\\ (+\ -\ -\ +)\end{matrix}\right\}\rightarrow(-\ +);\ (-);\ (+\ -\ -\ +),\ \text{etc.} \qquad [8b]$$

This is easier to program in an algorithm than it is to express in terms of probability densities. It allows the growth of chains of increasing length by using the active monomers in such a way that $\Delta\rho(-\mathbf{S})$ is positively driven by $\rho(+\mathbf{S})$ (where $\mathbf{S}$ is a vector $S_1 \dots S_N$). In general terms, let us introduce a vector notation for partitions of the set of spins $S_1 \dots S_N$:

$$(S_1 \dots S_j\ S_{j+1} \dots S_N) = (\mathbf{S}_1, \mathbf{S}_2),$$

where $\mathbf{S}_1 = (S_1 \dots S_j)$, $\mathbf{S}_2 = (S_{j+1} \dots S_N)$, etc. That is, we can describe $\rho(S_1 \dots S_N)$ in terms of its partitions into p groups of i_N spins

$$S_1 \dots S_N = \mathbf{S} = (S_1 \dots S_{i_1};\ S_{i_1+1} \dots S_{i_2};\ S_{i_2+1} \dots S_{i_3} \dots)$$
$$= (\mathbf{S}_1, \mathbf{S}_2, \mathbf{S}_3 \dots \mathbf{S}_p), \qquad [9]$$

where

$$\sum_n^p i_n = N. \qquad [10]$$

Now, we describe processes such as 8 by the equation

$$\Delta\rho_{\text{conj}}(\mathbf{S}_1, \mathbf{S}_2) = \sum_{S_0, S_j} k\,\rho(\mathbf{S}_1)\,\rho(\mathbf{S}_2)\,\rho(\mathbf{S}_0, -\mathbf{S}_1, -\mathbf{S}_2, \mathbf{S}_3)$$

$$\Delta\rho_{\text{conj}}(\mathbf{S}_1) = -\Delta\rho_{\text{conj}}(\mathbf{S}_1, \mathbf{S}_2) = \Delta\rho_{\text{conj}}(\mathbf{S}_2) \qquad [11]$$

for all possible sets of pairs S_1, S_2.

We especially allow processes that increase the total length of chains such as

$$(+\ -\ -\ +);\ \ (-\ +\ +);\ \ (+\ -\ +\ -)\rightarrow$$

$$\left\{\begin{matrix}(+\ -\ -\ +)\ \ (-\ +\ +)\\ (+\ -\ +\ -)\end{matrix}\right\}\rightarrow(+\ -\ -\ +\ -\ +\ +);\ (+\ -\ +\ -). \qquad [12]$$

For these,

$$\Delta\rho_{\text{conj}}(S_0, S_1, S_2, S_3) = k\rho(-S_1, -S_2)\rho(S_0, S_1)\rho(S_2, S_3) \qquad [13]$$

with, again, the appropriate $\Delta\rho$ values for the constituent molecules as well to allow conservation of monomers. (*iv*) Finally, to avoid indefinite growth and to allow for "mutation," we must build in an error rate. This can take several forms, and I may have chosen too special a one, but until actual simulations are carried out, let us propose that between conjugations, we allow a small percentage of

$$S_1S_2 \dots S_j \dots S_N \rightarrow S_1S_2 \dots -S_j \dots S_n; \qquad [14]$$

i.e., we will set up a density diffusion via

$$\Delta\rho(S_1 \dots S_j \dots S_N)$$
$$= \sum -\varepsilon[\rho(S_1 \dots, S_j, \dots S_N) - \rho(S_1, -S_j, \dots S_N)]. \qquad [15]$$

It may also be useful to allow for a rate of breakage and of erroneous transcription; in fact, I would prefer an algorithm that contained breakage, but 14 should be adequate to move us occasionally out of local minima of the death function.

Let us summarize the algorithm. We start, according to *ii*, with a few two- or three-base polymers, being sure to include both + + and + − sequences. We then subject them to a series of temperature cycles as follows:

(*1*) Add $2s$ monomers, in random proportion + and −.

(*2*) Allow conjugation between randomly chosen chains. An algorithm might be to make randomly chosen pairings and test for fit starting at one end and conjugating when possible; if any unpaired chains remain, again pair these along with all unsaturated conjugated structures, test for fit, and so on for a few stages. This will drive the system very hard relative to nature, but I think not in an essentially unrealistic way.

(*3*) Split apart the resulting chains and apply D: First, for each chain, calculate the appropriate value of D. This will be of random sign and hence not a true death function. Also, absolute values of D will be bigger for larger chains. I believe it is appropriate to add a constant to D of order $-N$ (the probability of damage is of order size) so as to make most values negative. Then, randomly select chains to annihilate with probability

$$(1 - e^{-[JN + \sum_{ij} J_{ij}S_iS_j]}), \qquad [16]$$

where J_{ij} has a variance of order J and both are quite small. If 16 is less than 0, we should reproduce S rather than annihilating it with the appropriate probability. I am not sure that the normalization in the length is suitable but do not wish to introduce too many arbitrary parameters.

Finally, we introduce the radiation (*iv*) by reversing spins on all chains with a very small probability ε per site. This is repeated until, one hopes, clusters of chains of similar structure appear.

DISCUSSION

By this time, most of the motivation in setting up this model will have become clear. I hope that this model is capable of mimicking the behavior of the origin of molecular evolution, in the sense that a modern-day statistical physicist could describe as "being in the same universality class with the origin of life." That is, we cannot hope by the finiteness of our lives to work in the original time scale nor can we guess precisely the chemical nature of the original molecules or the actual boundary conditions and constraints which were present. What we can do is to attempt to show that in a well-defined mathematical model, which in principle contains no inherent fudge factors that prejudice the outcome, a transition such as that between inanimate molecules and life does occur. I would argue that

previous attempts to set up a model or description of this process have missed some essential features. In particular, "chance and necessity" alone will not do it, even aided by the idea of self-organization via dissipative structures. I argue that, in addition, chaos is a precondition: we require a survival probability that is a fixed but chaotic function of the molecular composition.

Hartman (20) [following Cairns-Smith (21)] has proposed a logically consistent scheme in which the primitive replicating stage is not chains of RNA having a linear array of different bases but layers of silicate minerals having a two-dimensional array of different ions. From the "universality class" point of view, this proposal is totally equivalent: the crucial stage requires conjugation symmetry and random interaction with the environment. I have a personal preference, based on Ockham's razor, for the present model, but, of course, cannot exclude any possible scenario *a priori*.

Given this "quenched chaos," I hope that we can model the evolution of metastable clusters of similar molecular chains or "species" in the Eigen sense and show that these species can occasionally radiate by mutation into other forms. We can also hope that species can find it possible to interact and combine or recombine, or even to devour each other. (The modeling of this stage will probably require further development of the scheme.)

The question then resolves itself into whether the computer program as outlined does indeed successfully lead to the outcome predicted on heuristic analogue grounds. This will be discussed elsewhere.

I am indebted to J. J. Hopfield and L. Orgel for extensive discussion of the subject of this paper and to F. E. Yates for introducing me to the general area discussed here. I thank H. Hartman for valuable discussion and for an early suggestion that spin glass is a system of biological interest. I also thank D. Rokhsar and D. Stein for discussion and communication of preliminary results. Some of this work was done while I was a Fairchild Scholar at the California Institute of Technology, and I wish to express my gratitude to the Fairchild Foundation and to the hospitality of the Institute.

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